OFFICE OF NAVAL RESEARCH

ANNUAL PROGRESS REPORT

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TITLE OF PROJECT: NEUROLOGICAL MECHANISMS IN EPILEPSY

Objectives: To study in unrestrained animals the role of various cerebral structures in the onset, spread and clinical manifestations of the epileptic attack. The relation between cerebellum and cortical motor areas will also be considered.

ABSTRACT OF RESULTS

(a) The present project was activated on November 1, 1953 and this report covers the summary of results up to date.

(b) 1. Relations Between Neocerebellum and Cortical Motor Areas. In 40 cats with permanently implanted electrodes, stimulation of the ansiform and paramedian lobule and lobulus simplex of the neocerebellum at threshold levels of excitation resulted in motor responses indistinguishable from those elicited from the cerebral motor area. When the cerebellum was stimulated with strengths of 20% to 40% above threshold, rebound responses resulted. Still greater intensities of stimulation evoked cerebellar seizures. The existence of two functionally different systems was postulated. One, having a lower threshold, resulted in coordinated motor responses upon stimulation. while the other elicited facilitory and inhibitory responses. No evidence was found for the existence of discrete representation of movements in the cerebellar hemispheres. Simultaneous stimulation of the cerebrum and cerebellum at threshold levels of excitation resulted in coordinated movements, with the motor effects from each area retaining their own distinctive characteristics. Stimulation of the cerebellum with subthreshold stimuli (25 to 90%), at constant or varying frequencies, resulted in no apparent change in the excitability of the cerebral motor area. In spite of marked postural effects resulting from ablation of the cerebellum, the character and threshold of the movements evoked from the cerebral motor area were essentially unchanged. In addition, the motor effects elicited from the cerebellar hemispheres seemed not to be significantly altered by destruction of the cerebral motor area.

2. Epileptic Mechanisms in the Monkey. In 16 monkeys needle and plate electrodes, totaling 24 to 30 leads, were permanently implanted within the brain for about a six month period. The following structures have been

studied: motor cortex, premotor area, septal area, amygdala, hippocampus, thalamus, and reticular substance. The electrical activity of 16 pairs of points has been simultaneously recorded through 16 channels. Mechanisms for onset and spread of post-discharges were analyzed.

Thresholds for movements, and for electrically evoked post-discharges have been determined. A study of parameters of stimulation in the unanesthetized monkey has been completed. A paper, which will be submitted for publication has been written; a summary follows:

1) Effects of altering parameters upon the threshold of motor and autonomic responses produced by electrical stimulation of different cortical and subcortical areas of the brain were studied in unanesthetized monkeys with permanently implanted electrodes.

2) Waves of 0.01 to 5.0 msec. of pulse duration, and frequency ranges of 10 to 5000 cycles per second were used.

3) Voltage and current of stimuli passing through the animal were simultaneously monitored and measured by a two channel cathode ray oscilloscope.

4) Pulse durations of 0.1 to 0.5 msec. were generally most effective in evoking both motor and autonomic responses.

5) The lowest threshold for both motor and autonomic responses occurred at frequencies of 100 to 250 cps. At higher frequencies a sharper increase in threshold values was observed in the case of autonomic responses. Variation in frequency of stimuli resulted in alteration of the type of motor responses; at low frequencies (up to 60 cps.) single contractions followed the rate of stimuli; at higher frequencies (60 to 500) smooth movements occurred; at very high frequencies (up to 5000) quick, jerky movements at onset of stimulation were observed.

6) Similar fundamental changes and at approximately the same critical frequencies were obtained from different, widely separated areas of the gray

and the white matter of both cortical and subcortical areas of the brain. The possible role of bulbar and spinal cord integrative mechanisms in producing these alterations in type of motor responses, by stimulation of a single point with varying frequencies, has been emphasized.

7) The effects of changes of polarity and wave forms of stimuli have been discussed.

8) Monopolar stimulation, with negative monophasic or biphasic square wave forms of 0.1 to 0.3 msec. duration, and frequency of 100 to 250 cps., are suggested as the most suitable stimulation parameters in evoking organized motor responses.

3. Influence of Various CO_2 Concentrations on Electrical Activity and Excitability of the Brain in the Waking Monkey. This study has been made in collaboration with Dr. Karl E. Schaefer and Charles R. Carey, from the U.S. Naval Medical Research Laboratory, New London Connecticut. The monkeys were operated in New Haven, and after preliminary tests, were sent to New London for study under CO_2. Later they were returned to New Haven to be tested again, and to perform histological analyses of the brains. The summary of this work is as follows:

Multilead electrodes were permanently implanted in monkeys, according to Delgado's technique, for a period of 1 to 3 months in order to study the action of 5%, 10%, 15% and 30% concentrations of CO_2 in the air upon the brain. The following areas were studied: motor cortex, occipital cortex, centrum medianum of the thalamus, hypothalamus, and reticular substance. The pattern of the spontaneous electrical activity of each of the areas of the brain, recorded on different days, proved to be rather constant throughout all the observation periods on air. After 10 minutes' exposure to 10%, 15% or 30% CO_2, there was a generalized slowing down and decrease in amplitude in monopolar recording of all the areas, with the exception of the hypothalamus, which seemed to be less

affected. With 10% and 15% CO_2, bipolar recordings of the hypothalamus and reticular substance showed increased occurrence of runs of 5-7 cps., of higher amplitude. This phenomenon was also seen when the animals were exposed to 5% CO_2. With 30% CO_2 there was an initial period of increased number of 5-7 cps., followed by a gradual disappearance of this activity. In some animals after 18 minutes of exposure to 15% CO_2, the reticular substance and later the hypothalamus showed bursts of 3 per second waves of 200-300 microvolts. These bursts were rather localized and only from time to time spread to more superficial structures. Threshold of electrical stimulation of the hypothalamus and reticular formation decreased under 10%, 15% and 30% CO_2. Thresholds in other areas of the brain showed variable changes.

PLANS FOR FUTURE:

Immediate: 1) Study of relationship between cerebellum and motor cortex will be continued. Possible relations between these structures and reticular substance and red nucleus will also be investigated.

2) Study of the above mentioned structures concerning epileptic mechanisms will continue. Occipital cortex will also be included.

3) The study of the influence of CO_2 on the excitability of the brain will be continued. The action of prolonged exposures to CO_2 will be considered.

Long range: Completion of the above mentioned plans will keep us busy for a long time. The main addition to the plan will be the study of the mechanisms of action of anti-epileptic drugs.

REPORTS AND PUBLICATIONS

1. Progress Report, July 1, 1954: Functional Correlations Between Motor Cortex and Cerebellum.
2. A Dissertation presented to the Faculty of Yale University for the Degree of Doctor of Philosophy, by Arnold Schulman, May 1954: A Study of Functional Correlations Between Motor Cortex and Cerebellum.
3. Delgado, J.M.R. and Schulman, A. Cerebro-neocerebellar correlations in the awake cat. Fed. Proc., 1955 (in press).
4. Carey, C.R., Schaefer, K.E., and Delgado, J.M.R. Influence of various CO_2 concentrations on electrical activity and excitability of the brain in the waking monkey. Fed. Proc., 1955 (in press).